Remarks

Double Patenting and Rejection of the claims under 35 USC §103:

Claims 1-3 and 5-9 have been rejected on the ground of non-statutory obviousness type double patenting as being unpatentable over claims 1, 2, 6, and 7 of U.S. Patent 5,744,335 in view of Wolfert et al. (Bioconjugate Chemistry 1999) and Leake et al. (US 2004/0224405).

Claims 5, 6, and 9 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Wolff et al. (U.S. Patent 5,744,335) in view of Wolfert et al (Bioconjugate Chem. 1999) and Pollard et al. (J Biol Chem, 1998, 27:7507-7511).

It is the Examiner's position that the instant claims are obvious over Wolff et al. (U.S. Patent 5,744,335) combined with Wolfert et al. (Bioconjugate Chemistry 1999 Vol. 10, p. 993-1000). '335 taught the use of an amphipathic compound with the DNA-binding protein, histone, to deliver a polynucleotide to a mammalian cell in vitro. '335 further teaches that the polynucleotide can be DNA or RNA, short (oligonucleotide) or long (plasmid). Wolfert et al. described several physical properties of DNA/polyvinylamine (pVA) complexes and other DNA/polycation complexes. Wolfert et al. do not mention histone or amphipathic compounds.

The instant application claims a composition comprising an amphipathic compound, pVA, and siRNA to deliver the siRNA to a mammalian cell in vitro. An siRNA is a short double strand RNA. The instant application further teaches that several amphipathic compounds, including the amphipathic compound taught by '335, when combined with pVA are effective siRNA transfection reagents.

It is the Examiner's position that it was obvious replace the histone of the amphipathic compound/histone/polynucleotide composition taught by '335 with the pVA cationic polymer taught by Wolfert et al. to form an siRNA transfection reagent. The Examiner states that Wolfert et al. teach that DNA/pVA complexes are suitable for intranuclear delivery and that '335 teaches that their amphipathic compound generally enhances transfection efficiency. It is the Applicants position that both of these statements are incorrect.

First, Wolfert et al. do not teach that DNA/pVA complexes are suitable for intranuclear *delivery*. Rather, Wolfert et al. teach that DNA/pVA complexes are suitable for intranuclear *transcription*. Wolfert et al. describe: a) condensation of plasmid DNA with pVA (page 999, column 1 paragraph 2), b) flocculation properties of DNA/pVA complexes (page 999, column 1 paragraph 3), c) decondensation of DNA/pVA complexes with pLAA (page 999, column 1 paragraph 4), and d) zeta-potential of DNA/pVA complexes (page 999, column 1 paragraph 5). Wolfert et al. further teach that, while DNA/pVA complexes microinjected directly into Xenopus oocyte nuclei are transcribed (page 999, column 2, paragraph 3), DNA/pVA complexes "gave no significant spontaneous transfection when applied to 293 cells in vitro" even though "Complexes based on all the other nonquaternized cationic homopolymers examined produced higher levels of gene expression." (page 999, column 2, paragraph 2). Microinjection was performed by "injection of polymer/DNA complexes directly into the nucleus of Xenopus oocytes" (page 997, column 1, last paragraph). Transcription following arrival in the nucleus is a distinct activity separate from cellular or nuclear delivery. Because Wolfert et al. injected the complexes directly into the nucleus, no *delivery* function can have been made or implied. On the contrary, Wolfert et al. specifically teach "DNA complexes formed using the short side-chain PVA.HCl gave no significant spontaneous transfection." (page 999, column 2, paragraph 2). In fact, Wolfert et al. teach that, of the nonquaternized cationic homopolymers tested, pVA was the least effective at transfection. This teaching contradicts the Examiner's statement that there is no disclosure of polyvinylamine being unsuitable for polynucleotide delivery. It is the Applicants' opinion that there is no motivation to utilize pVA as a polynucleotide transfection reagent based on the teaching of Wolfert et al.

Second, '335 teaches only that the DNA-binding protein histone enhances transfection efficiency of the various lipids and that histone plus amphipathic compound is an effective transfection reagent. There is no claim, either stated or implied, that the amphipathic compound of '335 and the instant application enhances transfection of polycations in general. '335 specifically teaches:

a) "A variety of amphipathic compounds can be used in conjunction with a DNA binding protein such as histone protein to mediate the transfer of the plasmid DNA into the cell." column 2 lines 40-43,

b) "In contrast to the use of previously described cationic liposomes, most of the novel amphipathic cationic compounds described above do not efficiently mediate the transfer of genes into cells when used alone. However, the use of histone proteins with these novel amphipathic cationic compounds enable the efficient gene transfer into a variety of mammalian cells with minimal cellular toxicity. Therefore, the use of histone proteins expands the range and types of cationic lipids that can be used for gene transfer." column 5 lines 16-24,

c) "Cells transfected with ternary DNA-binding protein-pDNA-lipofectin complexes had substantially increased luciferase and B-galactosidase expression compared to transfections using binary pDNA-lipofectin complexes." column 22 lines 36-40,

d) "Histone H1 increased the transfection efficiency of not only lipofectin but also other cationic lipid formulations including DOTAP, lipofectACE, and lipofectAMINE." column 22 lines 44-47, and,

e) "These results demonstrate that histone H1 increases the transfection efficiency for a wide variety of amphipathic compounds." column 24 lines 18-20.

Thus, the teaching of '335 is clearly that histone enhances the transfection ability of a variety of amphipathic compounds, and not that any particular amphipathic compound, including that of the instant application, enhances the transfection properties of various polycations.

As stated above, '335 teaches that histone/amphipathic complexes are effective transfection compositions for DNA or RNA and plasmids or oligonucleotides. Using the Examiner's reasoning, substitution of pVA for histone in a polynucleotide/amphipathic compound/polycation complex should be an effective plasmid transfection reagent because Wolfert et al. teach that pVA is a polynucleotide delivery agent (Examiner's position) and '335 supposedly teach that the amphipathic compound generally enhances transfection activity of polycations (Examiner's position). However, Applicants have shown that pVA + amphipathic compound (such as that of instant claim 2 and '335) + DNA is *not* an effective transfection reagent. Thus, the amphipathic compound of instant claim 2 does not generally enhance the transfection ability of any polycation and pVA will not substitute for histone in the complex taught by '335 to form a complex with the same transfection properties as the histone-containing complex. In addition, Applicants have provided with this letter a declaration showing that the composition taught by '335 is not an effective siRNA delivery agent, despite the teaching in the specification of '335 that the composition is useful for

delivery of oligonucleotides or RNA. It is the Applicants' opinion that these data demonstrate that the instant invention is not obvious over '335 taken in view of Wolfert et al. Applicants have amended claim 5 to clarify that the composition is an effective siRNA *delivery* composition. Support for the amendment can be found in the specification on page 4 lines 20-21. Applicants request reconsideration of the rejection.

The Examiner's rejections are now believed to be overcome by this response to the Office Action. In view of Applicants' amendment and arguments, it is submitted that claims 1-3 and 5-9 should be allowable.

Respectfully submitted,

/Kirk Ekena/

Kirk Ekena, Reg. No. 56,672
Mirus Bio Corporation
505 South Rosa Road
Madison, WI 53719
608-238-4400

I hereby certify that this correspondence is being transmitted to the USPTO on this date: Dec. 5, 2007 .

/Kirk Ekena/
Kirk Ekena